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Hydrogen exchange method to identify the protein targets of drugs

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It is essential to identify a drug's target(s) to better understand the mechanism of action and anticipate possible side effects. Identifying these target(s) is a significant challenge in drug discovery. The most commonly used approach to identify the protein targets of small bioactive molecules is to capture binding proteins by affinity chromatography. Although well established, the affinity-based methods have considerable drawbacks. Small bioactive molecules need to be attached covalently to a solid support, which may result in masking critical recognition site(s) for the target proteins, and extensive washes are required to minimize the contamination of non-specifically bound proteins. This decreases the likelihood of identifying weakly bound proteins that may play significant roles in the pharmacological actions of small bioactive molecules. We propose here a new approach that does not require the immobilization of drugs. Our method measures the thermodynamic stability of proteins in the presence and absence of a small molecule drug by monitoring the changes of hydrogen-deuterium exchange rates of histidine residues in varying concentrations of protein denaturant. Because binding of a small molecule to a protein usually enhances the thermodynamic stability of the protein, the experiment should identify the target proteins. The results from our proof-of-concept study will be presented, and the strategy for the target identification in a proteome-scale sample will be discussed.

Biography

Masaru Miyagi has Ph.D. degree in Protein Chemistry and Mass Spectrometry from Osaka University, Japan. He is Assistant Professor at Case Western Reserve University. His scientific interests are focused on understanding how proteins function in the living cell. He has published more than 75 papers in reputed journals and has been serving as an editorial board member of Journal of the Mass Spectrometry Society of Japan, Journal of Integrated OMICS, and The Open Spectroscopy Journal.

Apoptosis sensitization by Euphorbia factor L1 in ABCB1-mediated MDR K562/ADR cells

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In this report, reversal activities of Euphorbia factor L1 (EFL1) against ABCB1-mediated multidrug resistance (MDR) and apoptosis sensitization in K562/ADR cells are reported. EFL1 decreased the IC50 values of anticancer agents in K562/ADR cells over-expressing ABCB1. However, EFL1 did not change the IC50 values of anticancer agents in sensitive K562 cells. Additionally, EFL1 increased the intracellular accumulation of rhodamine 123 and doxorubicin in K562/ADR cells without affecting their accumulation in K562 cells. Furthermore, EFL1 sensitized the apoptosis triggered by vincristine in K562/ADR cells, as confirmed by Annexin V-FITC/PI detection and Western blot. At the same time, EFL1 did not influence the apoptosis induced by vincristine in K562 cells. Western blot results showed that EFL1 did not affect the phosphorylation level of AKT and ERK in K562 and K562/ADR cells. Finally, EFL1 did not down-regulate protein expression of ABCB1.

Biography

Zhang Received B.S. of Pharmaceutical Sciences and M.S. of Pharmacognosy from Peking University, Ph.D. of Oncology in Sun Yat-sen University. He has been a visiting scholar at Hong Kong Baptist University for one and a half years. He is currently Committee Member of the Society of Anti-Cancer Drugs, Chinese Anti-Cancer Association and Committee Member of Division of Tumor Pharmacology, Chinese Pharmacological Society. Dr. Zhang is devoted to find active natural products targeted ABCB1 (P-glycoprotein, main cause of multidrug resistance), receptor tyrosine kinase (RTK) and cell cycle check point. Awards The 3rd Prize of Chinese Medical Science Award, 2012.